Remarks/Arguments

Claim 39 is amended. This amendment is supported on the original disclosure, see for example, original claim 35. Claims 1-38 were cancelled previously. Claims 39-44 remain under consideration in the application.

Claim Rejections-35 USC 103

The claims are rejected as obvious over Shefer (US 20030232091) in view of Won et. al. (US 5,955,109), Shalita (Cutis, 1999 June; 63 (6): 349-54), and Sefton (US 6,262,117). For a claim to be obvious, the prior art must teach or suggest all claim limitations. MPEP 2142. Claim 1 is amended to read "[a] heterogeneous composition comprising: a multiplicity of solid particles containing tazarotene but not benzoyl peroxide; and benzoyl peroxide." None of the references teach or suggest the desirablility of the multiplicity of solid particles not containing benzoyl peroxide. In fact, the Office Action suggests the opposite by stating "a skilled artisan would have reasonable expectation of successfully producing a composition with controlled continuous, release of effective levels of retinol and other active agents over an extended period of time." This seems to indicate that the Office reads the prior art to suggest putting the retinol (tazarotene) with the other active agent (benzoyl peroxide) into the particles to achieve sustained release. But in the claims as amended, benzoyl peroxide is excluded from the particles, thus thwarting the purpose of achieving sustained release. Therefore, the claims are not obvious.

In view of the arguments and the amendments made herein, Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Please charge Deposit Account 01-0885 for any fees related to this response.

Respectfully submitted,

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Enclosure: Shalita, et al., "Tazarotene Gel is Safe and Effective in the Treatment. . .,"

Tazarotene gel is safe and effective in the treatment of acne vulgaris: A multicenter, double-blind, vehicle-controlled study

Alan R Shalita, Dan K Chalker, Russell F Griffith, Adelaide A Herbert, et al. **Cutis**. Chatham: Jun 1999. Vol. 63, Iss. 6; pg. 349, 6 pgs

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[Headnote]
Retinoids reverse the abnormal pattern of keratinization seen in acne vulgaris. Tazarotene is the first of a novel family of topical receptor-selective acetylenic retinoids. This study evaluates the safety and efficacy of topical tazarotene 0.1 % and 0.05% gels, in comparison to vehicle gel, applied once daily for 12 weeks, in the treatment of mild-to-moderate facial acne vulgaris. A total of 446 patients with facial acne vulgaris were enrolled, and 375 patients, ranging in age from 14 to 44 years, were evaluable in this multicenter, double-blind, randomized study In comparison to vehicle gel, treatment with tazarotene 0.1% gel resulted in significantly greater reductions in noninflammatory and total lesion counts at all followup visits, and inflammatory lesion counts at Week 12. Tazarotene 0.05% gel resulted in significantly greater reductions in noninflammatory and total lesion counts than vehicle gel at Weeks 8 and 12. At Week 12, treatment success rates were 68% and 51% for

[Headnote]
tazarotene 0.1% and 0.05%, respectively (40% for vehicle gel). Tazarotene gel was an effective, safe, and generally well-tolerated therapy for the treatment of acne vulgaris.

Retinoids are small-molecule hormones that regulate gene activity. Retinoids affect multiple biologic functions, including cell differentiation and proliferation,1 through regulation of specific genes via multiple nuclear receptors. There are six known retinoid receptors that belong to two families, the retinoic acid receptor family and the retinoid X receptor family.2 Each receptor family includes three subtypes: a, b, and g.2 The many retinoid receptors, coupled with the variety of possibilities for receptor functions, enable retinoids to mediate a wide range of biologic effects via a complex multiplicity of pathways.2 Compounds that elicit the full spectrum of retinoid biologic activities may show significant efficacy but be of limited clinical usefulness because of many toxic side effects.2 Tazarotene, the first of a novel class of retinoids, the acetylenic retinoids, was designed to be receptor-selective, binding only to retinoic acid receptors b and g, and activating only those associated pathways. Tazarotene, which is also approved for the treatment of plaque psoriasis, appears to modulate three main pathogenic features of psoriasis: abnormal differentiation and hyperproliferation of the keratinocyte3 and inflammation.4 Abnormal keratinization and inflammation are also involved in acne. When applied topically in the treatment of acne vulgaris, retinoids reversed the abnormal pattern of keratinization that leads to formation of microcomedones, the precursor acne lesions.5

This study evaluates the safety and efficacy of tazarotene 0.1% and 0.05% gels, in comparison to tazarotene vehicle gel, applied once daily for 12 weeks, in the treatment of acne vulgaris.

Materials and Methods

This was a multicenter, double-blind, randomized, parallel-group, vehicle-controlled comparison. Patients 14 years of age and older, with mild-to-moderate facial acne vulgaris, were randomly assigned to one of three treatment groups:

tazarotene 0.1 % gel, tazarotene 0.05% gel, or vehicle gel (control). Mild-to-moderate facial acne vulgaris was defined as: 10 to 60 inflammatory lesions (sum of papules and pustules); 25 to 200 noninflammatory lesions (open and closed comedones); and <= 6 nodular cystic lesions (=> 5 mm in diameter). The study was conducted in compliance with the Code of Federal Regulations for institutional review boards and with the Declaration of Helsinki, and written informed consent was obtained from each patient or legal guardian.

Patients were excluded from the study if their acne was known to be resistant to oral antibiotics, or if they were pregnant, nursing, or of childbearing potential and not using a reliable form of contraception. Also excluded were patients who had used antibiotics or other anti-acne medications within 4 weeks (for systemic therapy) or 14 days (for topical therapy) of study entry, systemic retinoids, or estrogens within 12 weeks of study entry (estrogen treatment for more than 12 weeks immediately preceding study entry did not exclude participation, provided such treatment was not discontinued during the study).

Medications were applied once daily (in the evening) for 12 weeks, at least 30 minutes after washing the face with a nonmedicated cleanser (Dove(R) cleanser; Lever Brothers Co). Compliance was monitored by return of the medication tubes dispensed at the previous visit. Other anti-acne medications (systemic or topical) were not allowed during the study. However, nonmedicated shampoos and nonmedicated cosmetics were allowed.

Patients were evaluated at Weeks 0 (baseline), 4, 8, and 12. The key efficacy measures were percent change from baseline in counts of facial acne lesions (open and closed comedones, papules, pustules, and nodules); the investigators' global evaluation of response to treatment (Table I); and treatment success rates (defined as a global evaluation of good or excellent response, or complete clearing). Other measures evaluated during the study included the overall clinical severity grade, and signs and symptoms. At their last visit, patients rated their overall impression of the cosmetic characteristics of their medication as highly favorable, favorable, neutral, slightly unfavorable, or highly unfavorable. They also rated their impression of the medication's texture, ease of application, appearance, and odor.

Pharmacokinetic Analysis-At two investigational sites, blood samples were collected at Weeks 0, 8, and 12 for determination of plasma concentrations of tazarotene and its primary metabolite, tazarotenic acid. Analysis of plasma samples was conducted at Oneida Research Services, Inc. (Whitesboro, NY).

Safety Analysis-Patients were monitored for signs and symptoms of clinical adverse events. Adverse events were graded for severity (mild, moderate, or severe), and assessed for relationship to the study treatment.

Blood and urine samples were obtained from all patients at Weeks 0, 8, and 12, and analyzed (SmithKline Beecham Clinical Laboratories, Van Nuys, CA) for hematology, blood chemistry, and urinalysis parameters. At each study visit, urine pregnancy tests were conducted on all females of child-bearing potential. (Note: Tazarotene is contraindicated in women who are or may become pregnant. Women of childbearing potential should be warned of the potential risk to the fetus and use adequate birth-control measures when using tazarotene.)

Statistical Analysis-Categorical demographic data (gender and race) were analyzed with the CochranMantel-Haenszel procedure, with investigator as the stratification parameter, while age was analyzed with two-way analysis of variance. Percent change from baseline in lesion variables was compared among the three treatment groups with two-way analysis of variance (including the effects of drug, investigator, and drugby-investigator interaction) using a rank transformation. Mean investigators' global evaluation data and treatment success rates were analyzed with the CochranMantel-Haenszel procedure. Between-group comparisons of lesion counts, global scores, and treatment success rates were performed with Fisher's protected least-significant-differences test. Pharmacokinetic and safety data were summarized with descriptive statistical methods. Statistical Analysis System VAX version 6.08 was used for the statistical analyses (SAS Institute, Inc., Cary, NC). Also, a Last Observation Carried Forward analysis was conducted on treatment-related adverse events over time. A p value < 0.05 was considered to be statistically significant for treatment differences.

Table I

Results

Population-A total of 446 patients were enrolled and 333 completed the 12-week course of treatment. Reasons for withdrawal included disqualification for protocol deviations (n = 10), discontinuation for administrative reasons such as lost to follow-up or use of concomitant medication (n = 72), and termination because of adverse events (n = 27) or

lack of efficacy (n = 4).

Efficacy Results-A total of 375 patients, ranging in age from 14 to 44 years (mean, 20.8 years), were evaluable and were included in the preferred analysis. There were no significant differences among the treatment groups in age, gender, or race distribution, nor in the baseline numbers of lesions (Table II).

Mean percent decreases from baseline in noninflammatory, inflammatory, and total lesion counts were statistically significant ($p < 0.001$) in all treatment groups at all follow-up visits. As illustrated in Figure 1, tazarotene 0.1% gel was significantly more effective than vehicle gel in decreasing noninflammatory and total lesion counts at all follow-up visits, and in decreasing inflammatory lesion counts at Week 12. Tazarotene 0.05% gel was significantly more effective than vehicle in decreasing noninflammatory and total lesion counts at Weeks 8 and 12. Tazarotene 0.1% gel was significantly more effective than tazarotene 0.05% gel at decreasing noninflammatory lesion counts at Weeks 4 and 12, and in decreasing total lesion counts at Week 12. Mean percent decreases at Week 12 for noninflammatory, inflammatory, and total lesions, respectively, were approximately 55, 42, and 52% in the tazarotene 0.1 % group; 45, 39, and 44% in the tazarotene 0.05% group; and 35, 30, and 33% in the vehicle group.

Treatment success (good or excellent global response, or complete clearing of acne) occurred at a significantly greater rate in the tazarotene 0.1% group compared with the vehicle group at Weeks 8 and 12, and compared with the tazarotene 0.05% group at Week 12 (Figure 2). Also, treatment with tazarotene 0.05% resulted in a significantly higher success rate compared with vehicle at Week 8. At Week 12, the treatment success rates were 68, 51, and 40% for the tazarotene 0.1%, 0.05%, and vehicle gels, respectively.

Cosmetic Acceptability-The assigned aqueous gel treatment was rated cosmetically acceptable (highly favorable, favorable, or neutral impression) by approximately 90% of patients in tazarotene 0.1% group, 85% in the tazarotene 0.05% group, and 84% of the vehicle group. The patients' evaluation of the following characteristics for the three treatment groups demonstrated the cosmetic acceptability: ease of application (99% of patients had a neutral, favorable, or highly favorable response), texture (75% of patients had neutral or better response), appearance (84% neutral or better response), and odor (89% neutral or better response).

Pharmacokinetic Analysis-A total of 112 patients had blood samples drawn for pharmacokinetic analysis. From this pool, samples from 34 patients were randomly selected for bioanalysis. Plasma concentrations of tazarotene and its primary metabolite, tazarotenic acid, were below the quantifiable limit (< 0.05 ng/ml) in 45 of the 54 samples from patients treated with tazarotene. (Twelve patients whose blood was selected for analysis were treated with vehicle.) Three patients treated with tazarotene had detectable concentrations of tazarotene (ranging from 0.06 to 0.22 ng/ml), and four patients treated with tazarotene had detectable concentrations of tazarotenic acid (ranging from 0.06 to 0.13 ng/ml). These results indicate very limited systemic exposure to the drug.

Table II

Safety Analysis-All 446 enrolled patients were exposed to study medication and were included in the safety analysis. Age range, mean age, gender, and race distribution were very similar to those for the preferred analysis, and did not differ significantly among the treatment groups.

Treatment-related adverse events consisted primarily of mildto-moderate local irritation, such as burning, desquamation, or dryness. The majority of treatmentrelated adverse events during the 12-week treatment period were graded as mild to moderate. No treatment-related serious adverse events were reported. An analysis of treatment-related adverse events over time revealed a peak occurrence of these local effects at Week 4 (range, 3.5% erythema with tazarotene 0.05%, to 13.6% burning with tazarotene 0.1%), followed by a slight decline by Week 12 (Figure 3).

Treatment-related withdrawals, due primarily to local irritation, occurred in 8.7% of patients (13 of 150 patients) in the tazarotene 0.1% group, 8.1% (12 of 148 patients) in the tazarotene 0.05% group, and in 1.4% (2 of 148 patients) in the vehicle group.

Hematology, blood chemistry, and urinalysis results showed no consistent, clinically significant, drugrelated effects, and no laboratory findings were reported as adverse events.

Comments

Acne vulgaris is a sebaceous follicle disorder with a multifactorial pathogenesis believed to involve probable genetic susceptibility, hormonal influences, overproduction of sebum, abnormal keratinization, bacterial proliferation, and inflammation.6-13 The first histologically visible change in acne is a disruption in the normal pattern of keratinization, resulting in dense, coherent squamae of keratinous material that accumulate to form a plug in the orifice of the follicle, leading to formation of the microcomedo. Sebum also accumulates, and the growing mass of keratinous and sebaceous material results in progression of the microcomedo to an open or closed comedo (noninflammatory acne). This environment is ideal for the proliferation of the anaerobic organism, Propionibacterium acnes, which releases chemotactic factors that may result in a neutrophil infiltrate, which in turn may induce rupture of the comedo and progression to a papule or pustule (inflammatory acne).

FIGURE 1.

Tazarotene topical gel acts against several factors that contribute to acne vulgaris. Preclinical studies of isolated human keratinocytes and intact rhino mouse hair follicles (which are grossly distended by accumulated keratin) reveal that the keratinization pattern is normalized and the coherence of follicular keratinocytes is decreased, thus achieving a comedolytic effect against existing comedones and preventing the development of new microcomedones (data on file, Allergan Inc). This may be the primary mechanism of action of tazarotene in the treatment of acne vulgaris. By suppressing the microcomedo (the precursor acne lesion) and clearing obstructed follicles, tazarotene indirectly hinders the development and progression of inflammatory acne. In addition, a direct anti-inflammatory effect is suggested by the inhibition of the expression of migration inhibitory factor-related protein type 8 (a presumed proinflammatory marker) in skin grafts (data on file, Allergan Inc), and of pro-inflammatory markers intercellular adhesion molecule type 1 and human lymphocyte antigen type DR in psoriatic patients.14

In the present study, the greatest improvement was observed in noninflammatory lesions, which is consistent with the putative direct comedolytic effect of tazarotene. Tazarotene 0.1% gel was statistically superior to vehicle at Weeks 4, 8, and 12, and tazarotene 0.05% gel was statistically superior to vehicle at Weeks 8 and 12. An effect against inflammatory acne, supported by reductions in inflammatory lesions, occurred later in the study and was statistically significant only for the 0.1% concentration. The efficacy of the tazarotene gels was also supported by statistically superior treatment success rates compared with vehicle. Efficacy was concentration-dependent, as demonstrated by significant differences favoring the 0.1% concentration over the 0.05% concentration in noninflammatory lesion reductions, total lesion reductions, global response scores, and treatment success rates at Week 12. Sixty-eight percent of tazarotene 0.1%-treated patients and 51% of tazarotene 0.05%-treated patients had good, excellent, or complete clearing responses (defined as treatment success) at the end of 12 weeks of treatment. (It should be noted that, in the United States, tazarotene gel is only approved for the treatment of acne vulgaris at a concentration of 0.1%.)

Tazarotene 0.1% and 0.05% aqueous gels were safe and shown to have acceptable tolerability profiles. Adverse events consisted primarily of concentrationdependent, mild-to-moderate local irritation, which was consistent with the known effects of topical retinoids, including tretinoin. Such irritation can be managed in ways similar to other retinoids: reducing treatment to every other day until skin "hardens" to the retinoid; reducing the strength of the treatment, from 0.1% gel to 0.05% gel until the skin adjusts; or a combination of the two.

FIGURE 2.

Pharmacokinetic analysis confirmed that systemic exposure to the drug was very limited. In this study, tazarotene aqueous gel was an efficacious, safe, and welltolerated therapy for the treatment of acne vulgaris.

FIGURE 3.

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